REMARKS

The Office Action

Claims 1-61 and 63-82 are pending. Claims 1-52 and 69-78 are withdrawn from consideration as being drawn to a non-elected invention. Claims 53-61, 63-68, and 79-82 are currently under examination. Claims 53, 56, 59, 63-68, and 79-82 stand rejected under 35 U.S.C. § 102(b). Claims 53, 57, 60, 63, 65-67, and 79-82 stand rejected under 35 U.S.C. § 102(e). Claim 64 stands rejected under 35 U.S.C. § 103. Each of these rejections is addressed in detail below.

Amendments to the claims

Claim 68 has been amended to recite the limitation that the responsive element is directly responsive to the transactivator polypeptide. Support for this amendment can be found throughout the specification, for example, at page 34, lines 21-24. Claim 53 has been amended to remove the second embodiment. Claims 54 and 55 have been amended to correct the inadvertent omission of the word "site" after splice acceptor. Support for this amendment can be found throughout the claims and the specification. Claim 56 has been amended to specify that the promoter is a yeast promoter and support for this amendment can be found throughout the specification, for example, at page 27, lines 20-22. No new matter is added by these amendments. Claims 1-52 and 69-78 have been cancelled to comply with MPEP § 821.01 for being drawn to a nonelected invention.

Rejections under 35 U.S.C. § 102(b) and 102(e)

Claims 53, 56, 59, 63-67, and 79-82 stand rejected under 35 U.S.C. § 102(b) for anticipation by Baetscher. Claim 68 stands rejected under 35 U.S.C. § 102(b) for anticipation by Brent. Claims 53, 57, 60, 63, 65-67, and 79-82 stand rejected under 35 U.S.C. § 102(e), for anticipation by Tessier-Lavigne. For clarity, each of these rejections is addressed on a claim by claim basis in detail below.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F. 2d 628, 631, 2 U.S.P.Q. 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Furthermore, both the elements themselves *as well as the arrangement of the elements* must be identical to the claimed invention. "The elements must be arranged as required by the claim...." *In re Bond*, 910 F.2d 831, 15 U.S.P.Q. 1566 (Fed. Cir. 1990).

Claim 53

Claim 53 is rejected under 35 U.S.C. § 102(b) as being anticipated by Baetscher and under 102(e) as being anticipated by Tessier-Lavigne. Claim 53 features nucleic acids that include a splice acceptor site, a reporter gene, a positive selection maker, and a

negative selection marker. Each of the nucleic acids of claim 53 features a positive selection marker operably linked to a regulatory element of a host cellular gene after the nucleic acid is contacted with a cell. Each of the nucleic acid molecules also features a negative selection marker and a reporter gene, at least one of which is operably linked to a regulatory element of a host cellular gene after the nucleic acid is contacted with a cell. Both the inclusion of these structural elements and their specified arrangement in the embodiments recited in claim 53 distinguish the nucleic acids of claim 53 from those disclosed in Baetscher.

Baetscher describes gene trap constructs that generally include a splice acceptor, an IRES, and a promoterless protein coding sequence encoding a positive and negative selection trait. The constructs described in Baetscher do not anticipate claim 53. The Examiner asserts that the general formula for the nucleic acid construct by Baetscher can be summarized as follows.

Splice acceptor--IRES--positive selection--negative selection--reporter

The Examiner states that "the retroviral vector further comprises selectable or assayable makers" citing, as evidence, column 8, lines 50-57. Applicant asserts that Baetscher does not describe vectors that "further comprise selectable or assayable markers" and that these markers are suggested as alternatives for the positive or negative selection markers. At column 10, lines 12-13, it states, "[T]the expression of positive/negative reporter *or* selectable marker genes can be detected.... (emphasis added)." Baetscher's construct

includes the possibility of using selectable markers as an alternative to positive or negative selection markers. Thus, the general formula of Baetscher is correctly characterized as follows:

Splice acceptor--IRES--positive selection (reporter)--negative selection(reporter)

This construct does not anticipate claim 53. Column 8, lines 50-57, merely describes a handful of detectable makers that *can* be used in lieu of positive or negative markers. Baetscher makes no mention of a single construct having a positive selection marker, a negative selection marker, and a reporter gene as claimed in the present invention, where the positive selection marker is operably linked to a regulatory element of a host cellular gene after the nucleic acid is contacted with a cell.

In addition, Baetscher fails to describe all of the structural elements, let alone their specified orientation, found in each embodiment recited in claim 53. In the first embodiment recited in amended claim 53, the negative and positive selection markers are immediately 3' to the splice acceptor site. Placement of the negative and positive selection markers immediately 3' to the splice acceptor site allows for efficient expression of these marker genes. In the second embodiment recited in amended claim 53, the reporter gene and the positive selection marker are operably linked to regulatory elements of a host cellular gene after the nucleic acid is contacted with a cell. Baetscher

does not describe a construct having a positive selection maker, a negative selection marker, and a reporter gene, where the reporter gene and a positive selection marker operably linked to regulatory elements of a host cellular gene. In the third embodiment recited in amended claim 53, the nucleic acid has a splice acceptor, an IRES, and a negative selection marker, a positive selection marker, and a reporter gene, where the negative and positive selection markers are operably linked to the host cell. Again, Baetscher does not describe a construct having all of these structural elements where the negative and positive selection markers are operably linked to the host cell. In the fourth embodiment recited in amended claim 53, the IRES is placed between the reporter gene and the cassette including the negative selection marker and positive selection marker. This orientation is also not described by Baetscher. In the fifth embodiment recited in amended claim 53, the cassette includes a recombinase signal sequence, which is not described by Baetscher. As quoted above, both the elements themselves *as well as the arrangement of the elements* must be identical to the claimed invention. "The elements must be arranged as required by the claim...." *In re Bond, supra.* Because of the differences between the elements and the arrangement of the elements of Baetscher's nucleic acid and those recited in claim 53, Baetscher cannot anticipate the claim and this rejection should be withdrawn.

Claim 53 is also rejected under § 102(e) for anticipation by Tessier-Lavigne. Tessier-Lavigne describes vectors for expressing gene products in vertebrate neurons.

Tessier-Lavigne describes a vector having, in 5' to 3' orientation, a splice acceptor, a reporter gene (β-galactosidase), a positive selection marker (Neomycin), an IRES, and an axon reporter coding sequence (PLAP), where the positive selection marker and the axon reporter coding sequence are under the transcriptional control of a host cell gene. This construct does not anticipate claim 53, because all of the nucleic acids of claim 53 include a negative selection marker, which is absent from this construct of Tessier-Lavigne.

The Examiner further states that the axon reporter coding sequence of Tessier-Lavigne can be substituted for a negative selection marker such as diptheria toxin. This combination results in a construct having, in 5' to 3' orientation, a splice acceptor, a reporter gene (β-galactosidase), a positive selection marker (Neomycin), an IRES, and a negative selection marker (diptheria toxin). This construct also does not anticipate claim 53. In the first embodiment recited in claim 53, the negative and positive selection markers are 5' to the IRES and the reporter gene. This placement of the negative and positive selection markers allows for efficient expression of these marker genes. In the second embodiment recited in amended claim 53, the IRES is immediately 3' to the splice acceptor site followed by a cassette having a negative selection marker, a positive selection marker, and a reporter gene. This positioning is particularly effective because the IRES allows for translation in any reading frame. The ability to generate polypeptides irrespective of the reading frame enhances the efficiency of expression of the negative selection marker, the positive selection marker, and the reporter gene. In the third

embodiment recited in amended claim 53, the IRES is 5' to the negative selection marker, positive selection marker and reporter gene, which is advantageous because the IRES allows for translation in any reading frame and enhances the efficiency of expression of the selection markers and reporter gene. In the fourth embodiment recited in amended claim 53, the IRES is 5' to both the negative and positive selection markers which, as described above, enhances the efficiency of expression of the negative and positive selection markers. In the fifth embodiment, the cassette includes a recombinase signal sequence, which is not described by Tessier-Lavigne.

In summary, Tessier-Lavigne does not describe constructs having a negative selection marker, as claimed in each of the nucleic acids of claim 53. Tessier-Lavigne also does not describe the orientation of each of the structural elements of the nucleic acids as claimed in claim 53, nor does Tessier-Lavigne recognize or suggest the advantages of such an arrangement of elements. Accordingly, Tessier-Lavigne cannot anticipate claim 53 and this rejection should be withdrawn.

Claim 56

Claim 56 is rejected for anticipation by Baetscher. Claim 56 features nucleic acids having, in a specified 5' to 3' sequence, the following structural elements: a splice acceptor site, a negative selection marker, a positive selection marker, and a reporter gene. Baetscher does not describe a nucleic acid having the identical structural elements

and the arrangement of the elements recited in claim 56. In the first and second embodiment recited in claim 56, the negative and positive selection markers are immediately 3' to the splice acceptor site. Baetscher's constructs do not include placement of the negative and positive selection markers immediately 3' to the splice acceptor site. This placement of the negative and positive selection markers allows for efficient expression of these marker genes. In the third embodiment recited in claim 56, as amended herein, the positive selection marker is 3' to a yeast promoter. Baetscher's constructs do not include a negative selection marker, a reporter gene, and positive selection marker, which is operably linked to a yeast promoter within the nucleic acid construct. The structural elements, as well as the specified order of the elements, of each of the nucleic acids recited in claim 56 are distinct from those found in Baetscher's nucleic acid. Therefore, Baetscher does not anticipate claim 56.

Claim 57 and 60

Claim 57, features nucleic acids of claim 53 or 56 and further includes a nucleic acid segment encoding a transactivator polypeptide. As an initial matter, claim 57 depends from claim 53, which as described in detail above, is not anticipated by Tessier-Lavigne. Claim 57 also depends from claim 56, which the Examiner did not reject under § 102(e) in view of Tessier-Lavigne. If all the limitations of the independent claim are not anticipated, then the dependent claim also cannot be anticipated.

The Examiner states that Tessier-Lavigne anticipates both claims 57 and 60 based on an asserted description of a nucleic acid having the following general formula:

Splice acceptor-reporter-positive marker-IRES-negative marker-transactivator.

Applicant respectfully disagrees with this basis for the 102(e) rejection. Applicant submits that the Examiner has mischaracterized Tessier-Lavigne's nucleic acid construct described at column 4, lines 33-65 (page 6 of the Office action). Here, Tessier-Lavigne describes a "binary system" (line 36) where the gene trap vectors includes one vector having a promoterless selectable marker and a transcription factor encoding sequence, which, upon integration into a gene of the host cell, is expressed under the transcriptional control of the gene. The vector that includes the targeted gene product is then introduced into the host cell under the operative control of a regulatory region that is activatable by the transcription factor. The targeted gene products include reporter genes such as PLAP and GFP or *alternatively*, if it is desired, to modify or kill the recipient host cell, a toxin such as diphtheria toxin can be used (see column 4, lines 62-65). Tessier-Lavigne's constructs are part of a "binary system" and teach the use of the reporter gene or the negative selection marker as *alternative* possibilities for the targeted gene product vector. The use of a single construct having the selectable marker, the transcription factor, the negative selection marker, and the reporter gene *in the same construct*, as recited in claim

57, is not described or suggested by Tessier-Lavigne. This rejection should be withdrawn.

Claim 60 is also not anticipated by Tessier-Lavigne for the reasons cited above. Claim 60 recites a nucleic acid having a positive selection marker, a negative selection marker and a nucleic acid segment encoding a transactivator polypeptide, where the positive and negative selection markers are operably linked to a host cellular gene after then nucleic acid is contacted with a cell. As described above, Tessier-Lavigne describes a binary system of gene trap vectors that includes one vector having a promoterless selectable marker and a transcription factor encoding sequence, which, upon integration into a gene of the host cell, is expressed under the transcriptional control of the gene and a second vector that includes the targeted gene product that is then introduced into the host cell under the operative control of a regulatory region that is activatable by the transcription factor. Tessier-Lavigne does not describe a single vector having a positive selection marker, a negative selection marker and a nucleic acid segment encoding a transactivator polypeptide, where the positive and negative selection markers are operably linked to a host cellular gene after then nucleic acid is contacted with a cell. As stated above, for an anticipation rejection, "[T]the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Furthermore, both the elements themselves *as well as the arrangement of the elements* must be identical to the claimed

invention. "The elements must be arranged as required by the claim...." *In re Bond*, 910 F.2d 831, 15 U.S.P.Q. 1566 (Fed. Cir. 1990).

Accordingly, claim 60 is not anticipated by Tessier-Lavigne and this rejection should be withdrawn.

Claim 59

Amended claim 59 features two nucleic acids that include all of the following structural elements in a specified 5' to 3' orientation: a splice acceptor site, a negative and a positive selection marker, and a reporter gene, where the positive selection marker is operably linked to a prokaryotic promoter. In both embodiments, the negative selection marker is positioned immediately 3' to the splice acceptor site. Here again, the positioning of the negative marker immediately after the splice acceptor site allows for efficient expression of the negative selection marker. Nucleic acid constructs with a negative selection marker immediately 5' to the splice acceptor site is not taught or suggested by Baetscher. Baetscher cannot anticipate claim 59 and this aspect of the rejection should be withdrawn.

Claims 63 –67 and 79-82

Claims 63 -67 are directed to vectors and cells that include the nucleic acids of claims 53, 56, 59, 60, or 61. Claims 79-82 are directed to nucleic acids of claims 53, 56, 59, 60, or 61 and recite specific negative selection markers (claim 79), positive selection

markers (claim 80), and reporter genes (claims 81-82). These claim further limit the independent claims which, based on the amendments and the arguments present above, are not anticipated by Baetscher or Tessier-Lavigne. Applicant notes that claim 60 is cancelled by the amendment herein and the Examiner did not find claim 61 to be anticipated or obvious in view of any of the references. If the independent claim is not anticipated, then any claim depending therefrom is not anticipated. The § 102(b) and (e) rejections as applied to these claims should be withdrawn.

Claim 68

Claim 68 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Brent et al. (U.S.P.N. 5,695,941; hereinafter "Brent"). The Examiner maintains this rejection because, according to the Examiner, Applicant's definition of transactivator polypeptide includes proteins that indirectly activate the transcription of a gene and this indirect activation includes the potential for the transactivator to act as two individual polypeptides. While Applicant disagrees, in order to expedite prosecution claim 68 has been amended to include the limitation that the responsive element is directly responsive to the transactivator polypeptide. In view of this amendment, this rejection may now be withdrawn.

Rejection of claim 64 under 35 U.S.C. § 103

Claim 64 stands rejected under 35 U.S.C. § 103 for obviousness over Tessier-Lavigne in view of Baetscher. Applicant assumes, based on the identification of claim 64 with an asterisk and the use of the singular phrase "the claim...is newly rejected by the combination of references," that the Examiner intended the rejection only for claim 64 and not claims 53, 56, 57, 59, 60, 63, 65-67, and 79-82 as listed on page 7 of the action. Applicant also notes that the Examiner has not produced a *prima facie* case of obviousness for claims 53, 56, 57, 59, 60, 63, 65-67, and 79-82. The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. Therefore, Applicant's response is directed only to the Examiner's rejection and assertions regarding the *prima facie* obviousness of claim 64.

The Examiner states that Tessier-Lavigne teaches the nucleic acid constructs to be used as gene trap vectors but does not teach the use of retroviral vectors. According to the Examiner, it would have been obvious to combine the teachings of Tessier-Lavigne with Baetscher, which allegedly teaches each of the elements set forth in the claimed nucleic acids to be used as gene trap vectors and further indicates that retroviral vectors are useful for the efficient delivery of the nucleic acid constructs into eukaryotic cells. Applicant respectfully disagrees.

Claim 64 is directed to a retroviral vector that includes the nucleic acid of claim 53, 56, 59, 60, or 61. As described above, the nucleic acids claimed in each of these independent claims are not described or suggested by Tessier-Lavigne or Baetscher. Each of the independent claims recite nucleic acids having structural elements or a specific 5' to 3' orientation of the elements that are not described or suggested in either of the two references relied upon to support the rejection. Also as described above, in each of the embodiments, the specific order of the elements is critical and advantageous to the function of that particular nucleic acid. Neither Tessier-Lavigne nor Baetscher recognizes the criticality of the elements in the order recited in the present claims nor do they suggest any advantage to arranging the elements in the order specified.

MPEP § 2143 sets forth the basic requirements for a prima facie case of obviousness as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

These criteria have not been met in the present rejection. Claim 64 is directed to a retroviral vector that includes the nucleic acid of claim 53, 56, 59, 60, or 61 and none of these nucleic acids are taught or suggested by the cited references. The Examiner's reliance on the general statement that the teachings of Tessier-Lavigne and Baetscher all relate to the construction of gene trap vectors is inapposite in this case because the claimed nucleic acids are not general gene trap vectors but particular nucleic acid constructs with specific elements in a specified orientation which are not taught or suggested by either of the references. The Examiner's assertion that the skilled artisan would have been motivated to construct a retroviral vector comprising the nucleic acid taught specifically by Tessier-Lavigne does not render claim 64 obvious because the nucleic acid of Tessier-Lavigne does not meet all the limitations of the nucleic acids of claims 53, 56, 59, 60, or 61. The Examiner's assertion fails to meet one of the three key criteria for a *prima facie* case of obviousness, namely that the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In sum, the insertion of the claimed nucleic acids into a retroviral vector cannot be rendered obvious if the nucleic acids themselves are not known or suggested by Tessier-Lavigne or Baetscher. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re*

Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, the rejection of claim 64 under § 103 should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for filing an Appeal Brief for one month, to and including July 27, 2005.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 27, 2005

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